REMARKS

Claims 1, 4-10, 14-22, 25-28, 31-34 and 36-38 are pending and under examination in the above-identified application. Claims 5, 7, 15, 17, 19, 32, and 34 are cancelled herein. Applicants reserve the right to pursue these claims in a later filed application claiming the benefit of priority of the above application. Claims 1, 6, 14, 18, 28, 33, 37 and 38 have been amended above. Support for the amendments to claims 1, 14 and 28 can be found in the specification at, for example, paragraphs [034], [035] and [056]. Accordingly, the amendments do not raise an issue of new matter and entry thereof is respectfully requested. Applicants have reviewed the rejections set forth in the Office Action mailed January 17, 2008, and respectfully traverse all grounds for the reason that follow.

Rejections Under 35 U.S.C. § 112, Second Paragraph

The rejection of claim 15 under 35 U.S.C. §112, second paragraph, as allegedly indefinite for failing to point out and distinctly claim the subject matter regarded as the invention is respectfully traversed. This rejection has been rendered moot by cancellation of claim 15 without prejudice and removal of the rejection is respectfully requested.

Rejections Under 35 U.S.C. § 103

Claims 1, 4-10, 14-22, 25-28, 31-34, 37 and 38 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Walt et al., U.S. Patent No. 6,327,410, (Walt '410) in view of Drmanac et al. (EP 0392546, published October 17, 1990).

The Office Action alleges that it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the microspheres of Walt '410 by attaching the genomic fragments encoded by identifier oligonucleotides as allegedly taught by Drmanac. Current Office Action mailed January 17, 2008, page 4. One of ordinary skill would have allegedly been motivated to do so for the benefit of low cost and high throughput sequence determination as allegedly taught by Drmanac. *Id.* It is further alleged to have been obvious to one of ordinary skill to encode the microspheres of Walt '410 with the identifier binding ligands of Drmanac for the expected benefit of fast and frugal data generation. *Id.*

It is respectfully submitted that the above-proposed amendments to base claims 1, 14, and 28, render this rejection moot. As amended, base claims 1 and 28, are directed to an array composition and a composition, respectively, each requiring first and second microspheres comprising a plurality of different target nucleic acids target nucleic acid molecules wherein said first microsphere comprises sequences from a first individual and a first identifier binding ligand which identifies said plurality of different target nucleic acid molecules from the first individual and a second microsphere comprising a plurality of different target nucleic acid molecules comprising sequences from a second individual and wherein said second microsphere further comprises a second, different identifier binding ligand which identifies said plurality of different target nucleic acid molecules analytes from said second individual, wherein said plurality of different target nucleic acid molecules analytes are covalently attached to each of said microspheres, and wherein said microspheres are randomly distributed on said surface.

Amended base claim 14 requires an array composition comprising a substrate with discrete sites each comprising a microsphere having a different identifier binding ligand and a plurality of different covalently attached target nucleic acid molecules comprising sequences from different individuals, wherein said different identifier binding ligands each identify said plurality of different target nucleic acid molecules from different individuals; wherein said discrete sites are at a density of about 10,000 to 1,000,000,000 discrete sites per cm^2.

1. All Limitations Requirement Not Met by Combination of Cited References

The factual inquiry into whether claimed subject matter would have been obvious includes a determination of: (1) the scope and content of the prior art; (2) the differences between the claimed subject matter and the prior art; (3) the level of ordinary skill in the art; and (4) secondary considerations (e.g., the problem solved) that may be indicia of (non)obviousness. *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 17-18 (1966).

A finding of obviousness is impossible where the combination of the prior art, even if supported by a motivation to combine, discloses all the limitations of the claims. *CFMT, Inc. v. YieldUp Int'l Corp.*, 349 F.3d 1333, 1342 (Fed. Cir. 2003) *See In re Gulack*, 703 F.2d 1381, 1385 n.9 (Fed. Cir. 1983); *In re Royka*, 490 F.2d 981, 985 (CCPA 1974) (obviousness requires a suggestion of all limitations in a claim).

Applying the above-cited legal standards to this rejection, the Walt '410 and Drmanac et al. references, even if they were supported by a motivation to combine, microspheres with a *plurality of different target nucleic acid molecules covalently attached to each individual microsphere* as required by the current claims. Drmanac expressly describes emulsion PCR conditions to accomplish the goal of attaching only a *single* fragment onto each bead:

> The requirement is that micro droplets of an amplification mixture *each containing either a single fragment or none* are enclosed into small spheres (pearls) formed of appropriate membranes (perhaps the semipermeable ones) together with DP conglomerates.

Paragraph spanning columns 12 and 13; see also, column 13, lines 27-28. The above-quoted requirement of a single fragment per bead is a perquisite for operability of Drmanac et al.'s Sequencing by Hybridization (SBH) approach, which is incapable of distinguishing two different sequences on a single microsphere. Drmanac et al. acknowledges the necessity of having different sequences on different beads to be distinguished (see for example, the paragraphs from column 6, line 39, through column 7, line 21 which describe the need to have "a given genomic fragment . . . in one hybridization spot" and the advantages of replacing hybridization spots with beads). In addition to not teaching or suggesting a plurality of different target nucleic acids per individual bead, Drmanac et al. do not teach or suggest the element of microspheres that encompass different target nucleic acids that include nucleic acid sequences from different individuals as claimed.

While *KSR* arguably loosened the application of teaching-suggestion-motivation analysis, the Supreme Court did not address, much less abrogate, the requirement that each element must be disclosed by the cited prior art references. See *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1734, 82 USPQ2d 1385, 1391 (2007). Accordingly, because the cited references cannot be combined to teach each element of the rejected base claims, the rejection of base claims 1, 14 and 28 as well as their corresponding dependent claims is not properly supported by these references.

2. Teaching Away from Cited Combination of Cited References

A reference teaches away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a

direction divergent from the path that was taken by the applicant. *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994); *see KSR*, 127 S. Ct. at 1739–40 (explaining that when the prior art teaches away from a combination, that combination is more likely to be nonobvious). Additionally, a reference may teach away from a use when that use would render the result inoperable. *McGinley v. Franklin Sports, Inc.*, 262 F.3d 1339, 1354 (Fed. Cir. 2001).

While Drmanac et al. appears to describe beads with nucleic acids, the methods are directed to methods of sequencing an individual genome with each bead containing only a single sequence not different sequences. As explained above, the methods disclosed by Drmanac et al. are incapable of distinguishing two different sequences on a single microsphere. Furthermore, the skilled person would be discouraged from combining Dramanac et al. with Walt '410 to allegedly arrive at an array with nucleic acids from different individuals because the very purpose of the single genome sequencing of Drmanac et al. would be confounded by the presence of polymorphisms in a mixed population from more than one individual. This would render the methods to which Drmanac is directed wholly inoperable. Thus, the Drmanac et al. reference discourages the skilled person from making the modifications involved in combining Drmanac et al. and Walt '410 to arrive at the claimed invention and, therefore, teaches way from the claimed invention.

In view of the above, it is respectfully submitted that the combination of Walt '410 and Drmanac et al. cannot render obvious claims 1, 4-10, 14-22, 25-28, 31-34, 37 and 38 under 35 U.S.C. § 103(a). Therefore, in light of the amendments and remarks this ground of rejection is moot and its withdrawal is respectfully requested.

CONCLUSION

In light of the Amendments and Remarks herein, Applicants submit that the claims are in condition for allowance and respectfully request a notice to this effect. Should the Examiner have any questions, she is invited to call the undersigned attorney.

To the extent necessary, a petition for an extension of time under 37 C.F.R. 1.136 is hereby made. Please charge any shortage in fees due in connection with the filing of this paper, including extension of time fees, to Deposit Account 500417 and please credit any excess fees to such deposit account.

Respectfully submitted,

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